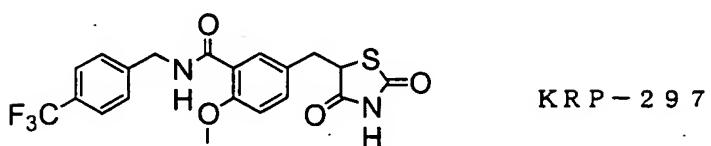
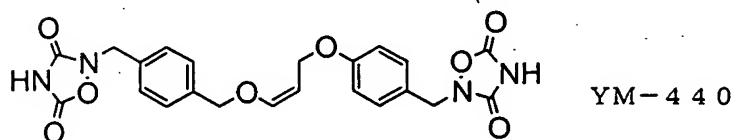
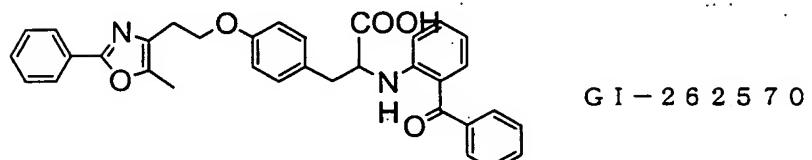
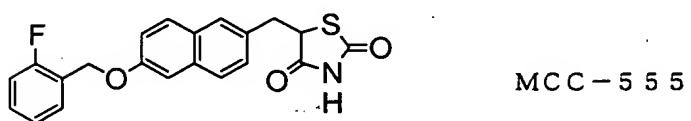
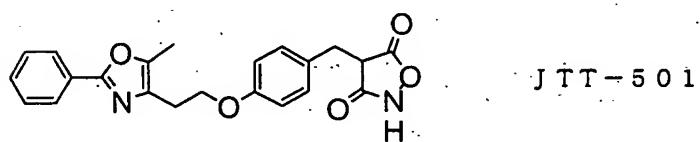
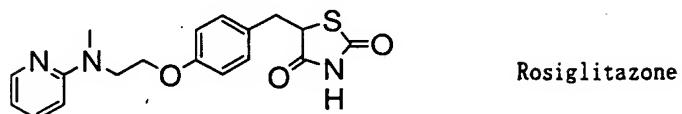
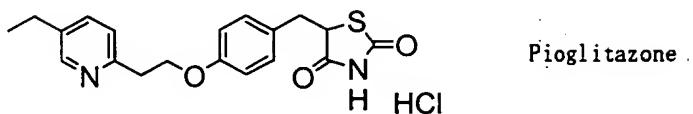


This listing of claims will replace all prior versions, and listings, of claims in the application:

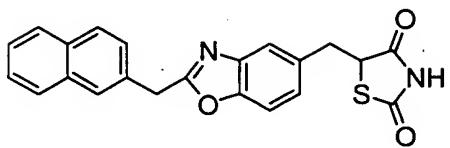
**Listing of Claims:**

1. **(Currently Amended)** A pharmaceutical composition comprising a diuretic and an insulin sensitizer in a ratio of amounts by weight of 1:200 to 200:1 and wherein said diuretic is selected from the group consisting ENaC inhibitors.
  
2. **(Original)** A pharmaceutical composition according to Claim 1 wherein said insulin sensitizer comprises one or more compounds selected from the group consisting of troglitazone and pioglitazone, rosiglitazone, JTT-501, MCC-555, GI-262570, YM-440, KRP-297, T-174, NC-2100, BMS-298585, AZ-242 and NN-622 represented by the formula below

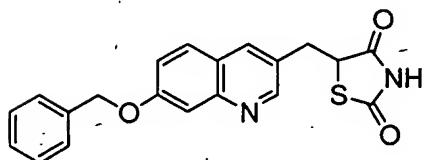
Appl. No. 10/606,632  
Reply to Office Action of October 21, 2004



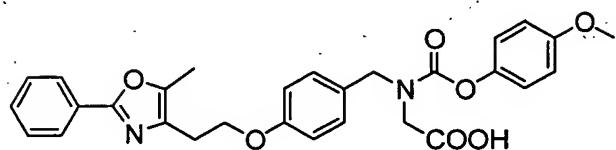
Appl. No. 10/606,632  
Reply to Office Action of October 21, 2004



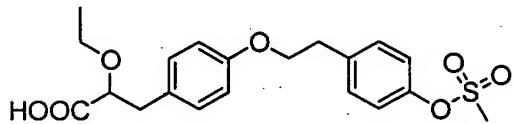
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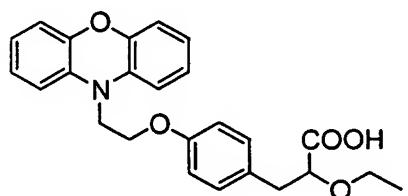
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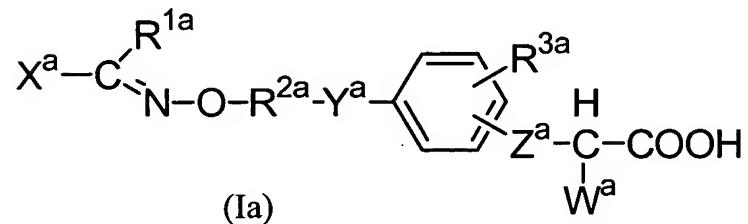
A Z - 2 4 2



N N - 6 2 2

5-[4-(6-Methoxy-1-methyl-1H-benzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione or a pharmacologically acceptable salt thereof,

a phenylalkylcarboxylic acid derivative having the general formula (Ia) below:



a pharmacologically acceptable salt thereof or a pharmacologically acceptable ester thereof

[wherein,

R<sup>1a</sup> represents a hydrogen atom or a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms,

R<sup>2a</sup> represents a straight- or branched-chain alkylene group having from 2 to 6 carbon atoms,

R<sup>3a</sup> represents (i) a hydrogen atom, (ii) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group

having from 1 to 4 carbon atoms, (v) a halogen atom, (vi) a nitro group, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below or (ix) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety,

$Z^a$  represents a single bond or a straight- or branched-chain alkylene group having from 1 to 6 carbon atoms,

$W^a$  represents (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a hydroxyl group, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (v) an amino group, (vi) a straight- or branched-chain monoalkylamino group having from 1 to 4 carbon atoms, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an N-alkyl-N-aryl amino group having a straight- or branched-chain alkyl group having from 1 to 4 carbon atoms and an aryl group

having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (ix) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below, (x) an aryloxy group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xi) an arylthio group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xii) an arylamino group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xiii) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xiv) an aralkyloxy group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xv) an aralkylthio group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xvi) an aralkylamino group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xvii) a 1-pyrrolyl group,

(xviii) a 1-pyrrolidinyl group, (xix) a 1-imidazolyl group, (xx) a piperidino group or (xxi) a morpholino group,

$X^a$  represents an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below or a 5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below,

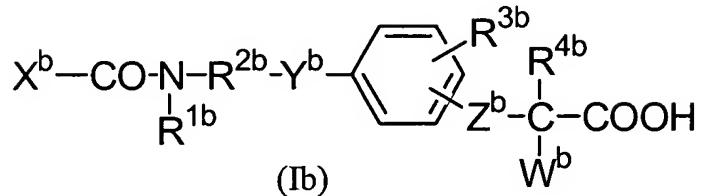
the substituent  $\alpha^a$  is selected from the group consisting of (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a straight- or branched-chain halogenated alkyl group having from 1 to 4 carbon atoms, (iii) a hydroxyl group, (iv) a straight- or branched-chain aliphatic acyloxy group having from 1 to 4 carbon atoms, (v) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (vi) a straight- or branched-chain alkylenedioxy group having from 1 to 4 carbon atoms, (vii) an aralkyloxy group having from 7 to 12 carbon atoms, (viii) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (ix) a straight- or branched-chain alkylsulfonyl group having from 1 to 4 carbon atoms, (x) a halogen atom, (xi) a nitro group, (xii) a straight-

or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (xiii) an aralkyl group having from 7 to 12 carbon atoms, (xiv) an aryl group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xv) an aryloxy group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvi) an arylthio group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4

carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvii) an arylsulfonyl group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xviii) an arylsulfonylamino group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms, and the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms), (xix) a 5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xx) a 5- to 10-membered monocyclic or bicyclic

heteroaromatic oxy group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxi) a 5- to 10-membered monocyclic or bicyclic heteroaromatic thio group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonyl group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms and (xxiii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonylamino group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms (the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms) and

$Y^a$  represents an oxygen atom, a sulfur atom or a group of formula:  $>N-R^{4a}$  (wherein  $R^{4a}$  represents a hydrogen atom, a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms or a straight- or branched-chain aliphatic acyl group having from 1 to 8 carbon atoms or an aromatic acyl group)], a amidocarboxylic acid derivative having the general formula (Ib) below:



a pharmacologically acceptable salt thereof or a pharmacologically acceptable ester thereof

[wherein,

$R^{1b}$  represents a hydrogen atom or a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms,

$R^{2b}$  represents a straight- or branched-chain alkylene group having from 1 to 6 carbon atoms,

$R^{3b}$  represents (i) a hydrogen atom, (ii) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (v) a halogen atom, (vi) a nitro group, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3

substituents  $\alpha^b$  mentioned below or (ix) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety,

$R^{4b}$  represents a hydrogen atom or a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms,

$Z^b$  represents a single bond or a straight- or branched-chain alkylene group having from 1 to 6 carbon atoms,

$W^b$  represents (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a hydroxyl group, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (v) an amino group, (vi) a straight- or branched-chain monoalkylamino group having from 1 to 4 carbon atoms, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an N-alkyl-N-arylamino group having a straight- or branched-chain alkyl group having from 1 to 4 carbon atoms and an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (ix) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3

substituents  $\alpha^b$  mentioned below, (x) an aryloxy group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xi) an arylthio group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xii) an arylamino group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xiii) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xiv) an aralkyloxy group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xv) an aralkylthio group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xvi) an aralkylamino group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xvii) a 1-pyrrolyl group, (xviii) a 1-pyrrolidinyl group, (xix) a 1-imidazolyl group, (xx) a piperidino group or (xxi) a morpholino group,  
 $\alpha^b$  represents an aryl group having from 6 to 10 carbon atoms

which may have from 1 to 3 substituents  $\alpha^b$  mentioned below or a 5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below,

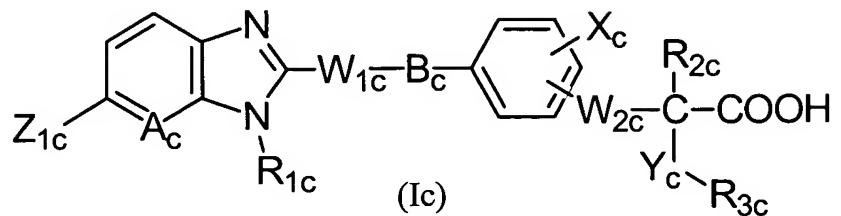
the substituent  $\alpha^b$  mentioned above is selected from the group consisting of (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a straight- or branched-chain halogenated alkyl group having from 1 to 4 carbon atoms, (iii) a hydroxyl group, (iv) a straight- or branched-chain aliphatic acyloxy group having from 1 to 4 carbon atoms, (v) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (vi) a straight- or branched-chain alkylenedioxy group having from 1 to 4 carbon atoms, (vii) an aralkyloxy group having from 7 to 12 carbon atoms, (viii) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (ix) a straight- or branched-chain alkylsulfonyl group having from 1 to 4 carbon atoms, (x) a halogen atom, (xi) a nitro group, (xii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (xiii) an aralkyl group having from 7

to 12 carbon atoms, (xiv) an aryl group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xv) an aryloxy group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvi) an arylthio group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvii) an arylsulfonyl group having from 6 to 10 carbon atoms (the aryl

moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xviii) an arylsulfonylamino group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms, and the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms), (xix) a 5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xx) a 5- to 10-membered monocyclic or bicyclic heteroaromatic oxy group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxi) a 5- to 10-membered monocyclic or bicyclic

heteroaromatic thio group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonyl group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms and (xxiii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonylamino group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms (the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms) and

$Y^b$  represents an oxygen atom, a sulfur atom or a group of formula:  $>N-R^{5b}$  (wherein  $R^{5b}$  represents a hydrogen atom, a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms or a straight- or branched-chain aliphatic acyl group having from 1 to 8 carbon atoms or an aromatic acyl group)], a  $\alpha$ -substituted carboxylic acid derivative having the general formula (Ic) below:



a pharmacologically acceptable ester thereof, a pharmacologically acceptable amide thereof or a pharmacologically acceptable salt thereof

[wherein,

R<sub>1c</sub>, R<sub>2c</sub> and R<sub>3c</sub> are the same or different, and each represents (i) a hydrogen atom, (ii) a C<sub>1</sub>-C<sub>6</sub> alkyl group, (iii) a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents α<sub>1c</sub> mentioned below), (iv) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having from 1 to 5 substituents α<sub>1c</sub> mentioned below on the aryl moiety), (v) a C<sub>1</sub>-C<sub>6</sub> alkylsulfonyl group, (vi) a C<sub>1</sub>-C<sub>6</sub> halogenoalkylsulfonyl group, (vii) a C<sub>6</sub>-C<sub>10</sub> arylsulfonyl group (optionally having from 1 to 5 substituents α<sub>1c</sub> mentioned below) or (viii) a C<sub>7</sub>-C<sub>16</sub> aralkylsulfonyl group (optionally having from 1 to 5 substituents α<sub>1c</sub> mentioned below on the aryl moiety),

A<sub>c</sub> represents a nitrogen atom or a =CH- group,

B<sub>c</sub> represents an oxygen atom or a sulfur atom,

$W_{1c}$  represents a  $C_1$ - $C_8$  alkylene group,

$W_{2c}$  represents a single bond or a  $C_1$ - $C_8$  alkylene group,

$X_c$  represents (i) a hydrogen atom, (ii) a  $C_1$ - $C_6$  alkyl group, (iii) a  $C_1$ - $C_6$  halogenoalkyl group, (iv) a  $C_1$ - $C_6$  alkoxy group, (v) a halogen atom, (vi) a hydroxyl group, (vii) a cyano group, (viii) a nitro group, (ix) a  $C_3$ - $C_{10}$  cycloalkyl group, (x) a  $C_6$ - $C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (xi) a  $C_7$ - $C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety), (xii) a  $C_1$ - $C_7$  aliphatic acyl group, (xiii) a  $C_4$ - $C_{11}$  cycloalkylcarbonyl group, (xiv) a  $C_7$ - $C_{11}$  arylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (xv) a  $C_6$ - $C_{17}$  aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety), (xvi) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (xvii) a carbamoyl group, (xviii) a  $C_7$ - $C_{11}$  arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety) or (xix) an amino group (optionally having one or two substituents  $\beta_c$  mentioned below),

$Y_c$  represents an oxygen atom or a  $S(O)_p$  group (wherein p is an integer of from 0 to 2),

$Z_{1c}$  represents (i) a hydrogen atom, (ii) a  $C_1-C_6$  alkyl group, (iii) a  $C_1-C_6$  alkoxy group, (iv) a  $C_1-C_6$  alkylthio group, (v) a halogen atom, (vi) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\alpha_1$  mentioned below), (vii) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below on the aryl moiety), (viii) a  $C_6-C_{10}$  aryloxy group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below), (ix) a  $C_7-C_{16}$  aralkyloxy group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below on the aryl moiety), (x) a  $C_3-C_{10}$  cycloalkyloxy group, (xi) a  $C_3-C_{10}$  cycloalkylthio group, (xii) a saturated heterocyclic oxy group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below), (xiii) a monocyclic heteroaromatic oxy group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below), (xiv) a  $C_6-C_{10}$  arylthio group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below), (xv) a  $C_7-C_{16}$  aralkylthio group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below on the aryl moiety), (xvi) a saturated heterocyclic thio group (optionally having from 1 to 5

substituents  $\alpha_{1c}$  mentioned below), (xvii) a monocyclic heteroaromatic thio group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below), (xviii) an amino group (optionally having one or two substituents  $\alpha_{1c}$  mentioned below) or (xix) a hydroxyl group,

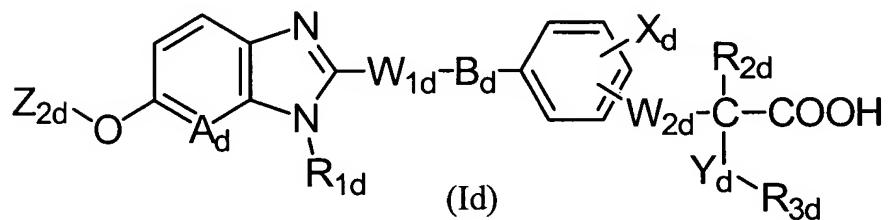
the substituent  $\alpha_{1c}$  represents (i) a C<sub>1</sub>-C<sub>6</sub> alkyl group, (ii) a C<sub>1</sub>-C<sub>6</sub> halogenoalkyl group, (iii) a C<sub>1</sub>-C<sub>6</sub> alkoxy group, (iv) a halogen atom, (v) a hydroxyl group, (vi) a cyano group, (vii) a nitro group, (viii) a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, (ix) a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (x) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety), (xi) a C<sub>1</sub>-C<sub>7</sub> aliphatic acyl group, (xii) a C<sub>4</sub>-C<sub>11</sub> cycloalkylcarbonyl group, (xiii) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (xiv) a C<sub>8</sub>-C<sub>17</sub> aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety), (xv) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (xvi) a carbamoyl group, (xvii) a C<sub>7</sub>-C<sub>11</sub>

arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety), (xviii) an amino group (optionally having one or two substituents  $\beta_c$  mentioned below) or (xix) a carboxyl group,

the substituent  $\beta_c$  represents (i) a  $C_1-C_{10}$  alkyl group, (ii) a halogen atom, (iii) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below), (iv) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below on the aryl moiety), (v) a  $C_1-C_7$  aliphatic acyl group, (vi) a  $C_7-C_{11}$  arylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below), (vii) a  $C_8-C_{17}$  aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below on the aryl moiety), (viii) a  $C_4-C_{11}$  cycloalkylcarbonyl group, (ix) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below), (x) a carbamoyl group or (xi) a  $C_7-C_{11}$  arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below on the aryl moiety) and

the substituent  $\gamma_c$  represents a  $C_1-C_6$  alkyl group, a  $C_1-C_6$

halogenoalkyl group, a halogen atom or a hydroxyl group],  
a  $\alpha$ -substituted carboxylic acid derivative having the  
general formula (Id) below:



a pharmacologically acceptable ester thereof, a pharmacologically acceptable amide thereof or a pharmacologically acceptable salt thereof

[wherein,

$R_{1d}$ ,  $R_{2d}$  and  $R_{3d}$  are the same or different, and each represents (i) a hydrogen atom, (ii) a  $C_1-C_6$  alkyl group, (iii) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\alpha_{1d}$  mentioned below), (iv) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\alpha_{1d}$  mentioned below on the aryl moiety), (v) a  $C_1-C_6$  alkylsulfonyl group, (vi) a  $C_1-C_6$  halogenoalkylsulfonyl group, (vii) a  $C_6-C_{10}$  arylsulfonyl group (optionally having from 1 to 5 substituents  $\alpha_{1d}$  mentioned below)

or (viii) a C<sub>7</sub>-C<sub>16</sub> aralkylsulfonyl group (optionally having from 1 to 5 substituents α<sub>1d</sub> mentioned below on the aryl moiety),

A<sub>d</sub> represents a nitrogen atom or a =CH- group,

B<sub>d</sub> represents an oxygen atom or a sulfur atom,

W<sub>1d</sub> represents a C<sub>1</sub>-C<sub>8</sub> alkylene group,

W<sub>2d</sub> represents a single bond or a C<sub>1</sub>-C<sub>8</sub> alkylene group,

X<sub>d</sub> represents (i) a hydrogen atom, (ii) a C<sub>1</sub>-C<sub>6</sub> alkyl group, (iii) a C<sub>1</sub>-C<sub>6</sub> halogenoalkyl group, (iv) a C<sub>1</sub>-C<sub>6</sub> alkoxy group, (v) a halogen atom, (vi) a hydroxyl group, (vii) a cyano group, (viii) a nitro group, (ix) a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, (x) a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below), (xi) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below on the aryl moiety),

(xii) a C<sub>1</sub>-C<sub>7</sub> aliphatic acyl group, (xiii) a C<sub>4</sub>-C<sub>11</sub>

cycloalkylcarbonyl group, (xiv) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group

(optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below), (xv) a C<sub>8</sub>-C<sub>17</sub> aralkylcarbonyl group (optionally having from 1 to 5

substituents β<sub>d</sub> mentioned below on the aryl moiety), (xvi) a

monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below), (xvii) a carbamoyl

group, (xviii) a C<sub>7</sub>-C<sub>11</sub> arylaminocarbonyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below on the aryl moiety) or (xix) an amino group (optionally having one or two substituents β<sub>d</sub> mentioned below),

Y<sub>d</sub> represents an oxygen atom or a S(O)<sub>p</sub> group (wherein p is an integer of from 0 to 2),

Z<sub>2d</sub> represents a saturated heterocyclic group (optionally having from 1 to 5 substituents α<sub>1d</sub> mentioned below) or a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents α<sub>2d</sub> mentioned below),

the substituent α<sub>1d</sub> represents (i) a C<sub>1</sub>-C<sub>6</sub> alkyl group, (ii) a C<sub>1</sub>-C<sub>6</sub> halogenoalkyl group, (iii) a C<sub>1</sub>-C<sub>6</sub> alkoxy group, (iv) a halogen atom, (v) a hydroxyl group, (vi) a cyano group, (vii) a nitro group, (viii) a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, (ix) a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below), (x) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below on the aryl moiety), (xi) a C<sub>1</sub>-C<sub>6</sub> aliphatic acyl group, (xii) a C<sub>4</sub>-C<sub>11</sub> cycloalkylcarbonyl group, (xiii) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below), (xiv) a C<sub>8</sub>-C<sub>17</sub> aralkylcarbonyl

group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below on the aryl moiety), (xv) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below), (xvi) a carbamoyl group, (xvii) a C<sub>7</sub>-C<sub>11</sub> arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below on the aryl moiety), (xviii) an amino group (optionally having one or two substituents  $\beta_d$  mentioned below) or (xix) a carboxyl group,

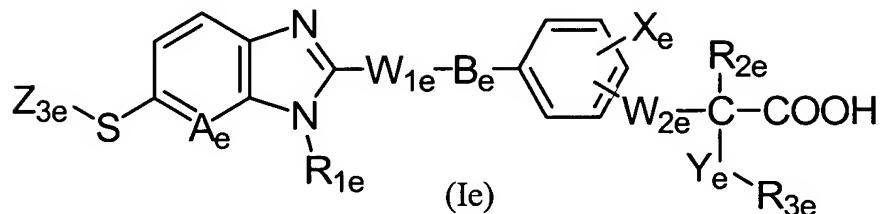
the substituent  $\alpha_{2d}$  represents (i) a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, (ii) a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below), (iii) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below on the aryl moiety), (iv) a C<sub>1</sub>-C<sub>7</sub> aliphatic acyl group, (v) a C<sub>4</sub>-C<sub>11</sub> cycloalkylcarbonyl group, (vi) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below), (vii) a C<sub>8</sub>-C<sub>17</sub> aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below on the aryl moiety), (viii) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below) or (ix) a C<sub>7</sub>-C<sub>11</sub>

arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below on the aryl moiety),

the substituent  $\beta_d$  represents (i) a  $C_1-C_{10}$  alkyl group, (ii) a halogen atom, (iii) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below), (iv) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below on the aryl moiety), (v) a  $C_1-C_7$  aliphatic acyl group, (vi) a  $C_7-C_{11}$  arylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below), (vii) a  $C_8-C_{17}$  aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below on the aryl moiety), (viii) a  $C_4-C_{11}$  cycloalkylcarbonyl group, (ix) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below), (x) a carbamoyl group or (xi) a  $C_7-C_{11}$  arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below on the aryl moiety) and

the substituent  $\gamma_d$  represents a  $C_1-C_6$  alkyl group, a  $C_1-C_6$  halogenoalkyl group, a halogen atom or a hydroxyl group] and a  $\alpha$ -substituted carboxylic acid derivative having the

general formula (Ie) below:



a pharmacologically acceptable ester thereof, a pharmacologically acceptable amide thereof or a pharmacologically acceptable salt thereof

[wherein,

$R_{1e}$ ,  $R_{2e}$  and  $R_{3e}$  are the same or different, and each represents (i) a hydrogen atom, (ii) a  $C_1-C_6$  alkyl group, (iii) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below), (iv) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below on the aryl moiety), (v) a  $C_1-C_6$  alkylsulfonyl group, (vi) a  $C_1-C_6$  halogenoalkylsulfonyl group, (vii) a  $C_6-C_{10}$  arylsulfonyl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below) or (viii) a  $C_7-C_{16}$  aralkylsulfonyl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below on the aryl moiety),

A<sub>e</sub> represents a nitrogen atom or a =CH- group,  
B<sub>e</sub> represents an oxygen atom or a sulfur atom,  
W<sub>1e</sub> represents a C<sub>1</sub>-C<sub>8</sub> alkylene group,  
W<sub>2e</sub> represents a single bond or a C<sub>1</sub>-C<sub>8</sub> alkylene group,  
X<sub>e</sub> represents (i) a hydrogen atom, (ii) a C<sub>1</sub>-C<sub>6</sub> alkyl group,  
(iii) a C<sub>1</sub>-C<sub>6</sub> halogenoalkyl group, (iv) a C<sub>1</sub>-C<sub>6</sub> alkoxy group, (v)  
a halogen atom, (vi) a hydroxyl group, (vii) a cyano group,  
(viii) a nitro group, (ix) a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, (x) a C<sub>6</sub>-C<sub>10</sub>  
aryl group (optionally having from 1 to 5 substituents β<sub>e</sub>  
mentioned below), (xi) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having  
from 1 to 5 substituents β<sub>e</sub> mentioned below on the aryl moiety),  
(xii) a C<sub>1</sub>-C<sub>7</sub> aliphatic acyl group, (xiii) a C<sub>4</sub>-C<sub>11</sub>  
cycloalkylcarbonyl group, (xiv) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group  
(optionally having from 1 to 5 substituents β<sub>e</sub> mentioned below),  
(xv) a C<sub>8</sub>-C<sub>17</sub> aralkylcarbonyl group (optionally having from 1 to 5  
substituents β<sub>e</sub> mentioned below on the aryl moiety), (xvi) a  
monocyclic heteroaromatic carbonyl group (optionally having from  
1 to 5 substituents β<sub>e</sub> mentioned below), (xvii) a carbamoyl  
group, (xviii) a C<sub>7</sub>-C<sub>11</sub> arylaminocarbonyl group (optionally having  
from 1 to 5 substituents β<sub>e</sub> mentioned below on the aryl moiety)

or (xix) an amino group (optionally having one or two substituents  $\beta_e$  mentioned below),

$Y_e$  represents an oxygen atom or a  $S(O)_p$  group (wherein p is an integer of from 0 to 2),

$Z_{3e}$  represents (i) a  $C_1-C_6$  alkyl group, (ii) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below), (iii) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below on the aryl moiety), (iv) a  $C_3-C_{10}$  cycloalkyl group or (v) a saturated heterocyclic group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below),

the substituent  $\alpha_{1e}$  represents (i) a  $C_1-C_6$  alkyl group, (ii) a  $C_1-C_6$  halogenoalkyl group, (iii) a  $C_1-C_6$  alkoxy group, (iv) a halogen atom, (v) a hydroxyl group, (vi) a cyano group, (vii) a nitro group, (viii) a  $C_3-C_{10}$  cycloalkyl group, (ix) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below), (x) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below on the aryl moiety), (xi) a  $C_1-C_7$  aliphatic acyl group, (xii) a  $C_4-C_{11}$  cycloalkylcarbonyl group, (xiii) a  $C_7-C_{11}$  arylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below), (xiv) a  $C_8-C_{17}$  aralkylcarbonyl

group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below on the aryl moiety), (xv) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below), (xvi) a carbamoyl group, (xvii) a C<sub>7</sub>-C<sub>11</sub> arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below on the aryl moiety), (xviii) an amino group (optionally having one or two substituents  $\beta_e$  mentioned below) or (xix) a carboxyl group,

the substituent  $\beta_e$  represents (i) a C<sub>1</sub>-C<sub>10</sub> alkyl group, (ii) a halogen atom, (iii) a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below), (iv) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below on the aryl moiety), (v) a C<sub>1</sub>-C<sub>6</sub> aliphatic acyl group, (vi) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below), (vii) a C<sub>8</sub>-C<sub>17</sub> aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below on the aryl moiety), (viii) a C<sub>4</sub>-C<sub>11</sub> cycloalkylcarbonyl group, (ix) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below),

(x) a carbamoyl group or (xi) a C<sub>7</sub>-C<sub>11</sub> arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below on the aryl moiety) and

the substituent  $\gamma_e$  represents a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> halogenoalkyl group, a halogen atom or a hydroxyl group].

**3. (Currently Amended)** A pharmaceutical composition according to Claim 2, wherein said diuretic ~~comprises one or more compounds selected from the group consisting of acetazolamide, azosemide, is amiloride[[],] isosorbide, etacrynic acid, potassium canrenoate, chlortalidone, cyclopentiazide, spironolactone, torasemide, triamterene, trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, piretanide, bumetanide, furosemide, benzylhydrochlorothiazide, penflutizide, methyclothiazide, metolazone and mefruside or selected from the group consisting of ENaC inhibitors.~~.

**4. (Original).** A pharmaceutical composition according to Claim 1 wherein said insulin sensitizer is 5-[4-(6-methoxy-1-methyl-1H-benzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione or a pharmacologically acceptable salt thereof.

5. (Currently Amended) A pharmaceutical composition according to Claim 1, wherein said diuretic ~~comprises one or more compounds selected from the group consisting of acetazolamide, azosemide, amiloride, isosorbide, etacrynic acid, potassium canrenoate, chlortalidone, cyclopentiazide, spironolactone, torasemide, is triamterene[[],] trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, piretanide, bumetanide, furosemide, benzylhydrochlorothiazide, penflutizide, methyclothiazide, metolazone and mefruside or selected from the group consisting of ENaC inhibitors.~~.

6. (Original) A pharmaceutical composition according to Claim 4, wherein said diuretic is amiloride.

7. (Original) A pharmaceutical composition according to Claim 1, wherein said diuretic is amiloride.

8. (Withdrawn) A method for the treatment or prophylaxis of diabetes mellitus, wherein said treatment or prophylaxis comprises administration in effective amounts, of the pharmaceutical composition of claim 1 a diuretic and an insulin

~~sensitizer in a weight ratio of 1.200 to 200.1, simultaneously or at suitable intervals.~~

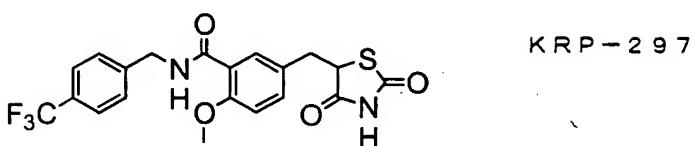
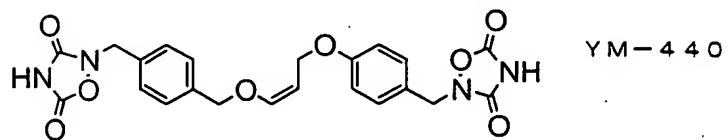
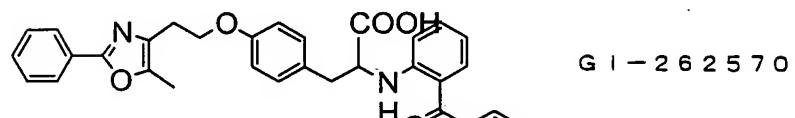
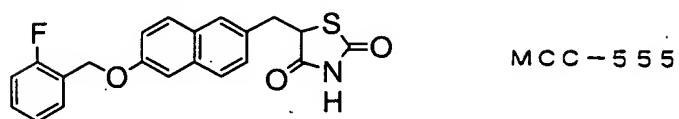
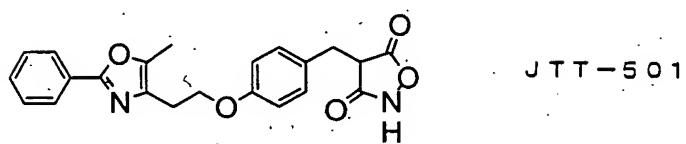
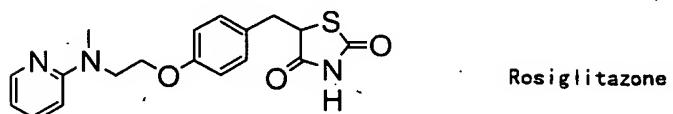
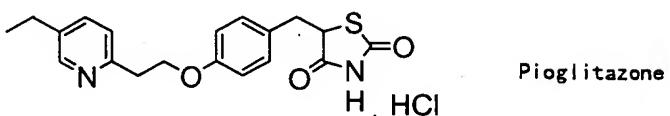
9. (Withdrawn) A method according to claim 8, wherein said diuretic comprises one or more compounds selected from the group consisting of ~~acetazolamide, azosemide, amiloride, isosorbide, etacrynic acid, potassium canrenoate, chlortalidone, cyclopentiazide, spironolactone, torasemide, and triamterene~~ [ , ] trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, piretanide, bumetanide, furosemide, benzylhydrochlorothiazide, penflutizide, methyclothiazide, metolazone and mefruside or said diuretic comprises one or more compounds selected from the group consisting of ENaC inhibitors.

10. (Withdrawn) A method according to claim 8, wherein said administration is simultaneous.

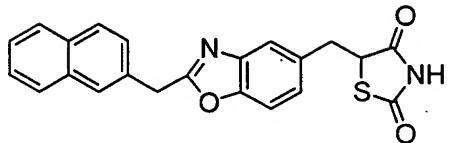
11. (Withdrawn) A method according to claim 8, wherein said administration is at a suitable interval.

12. (Withdrawn) A method according to claim 8, wherein said insulin sensitizer comprises one or more compounds selected from the group consisting of troglitazone and pioglitazone, rosiglitazone, JTT-501, MCC-555, GI-262570, YM-440, KRP-297, T-174, NC-2100, BMS-298585, AZ-242 and NN-622 represented by the formulae below,

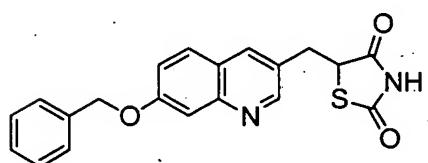
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Reply to Office Action of October 21, 2004



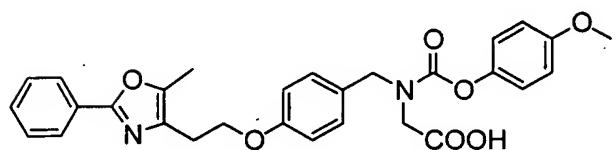
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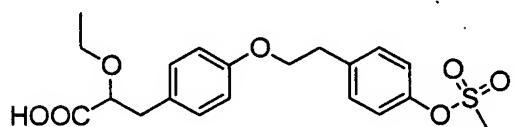
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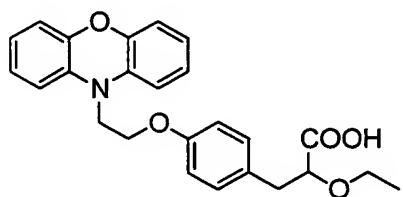
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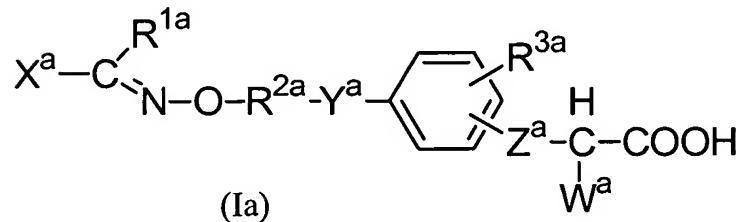
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5-[4-(6-Methoxy-1-methyl-1H-benzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione or a pharmacologically acceptable salt thereof,

a phenylalkylcarboxylic acid derivative having the general formula (Ia) below:



a pharmacologically acceptable salt thereof or a pharmacologically acceptable ester thereof  
[wherein,

R<sup>1a</sup> represents a hydrogen atom or a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms,

R<sup>2a</sup> represents a straight- or branched-chain alkylene group having from 2 to 6 carbon atoms,

R<sup>3a</sup> represents (i) a hydrogen atom, (ii) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group

having from 1 to 4 carbon atoms, (v) a halogen atom, (vi) a nitro group, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below or (ix) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety,

$Z^a$  represents a single bond or a straight- or branched-chain alkylene group having from 1 to 6 carbon atoms,

$W^a$  represents (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a hydroxyl group, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (v) an amino group, (vi) a straight- or branched-chain monoalkylamino group having from 1 to 4 carbon atoms, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an N-alkyl-N-arylamino group having a straight- or branched-chain alkyl group having from 1 to 4 carbon atoms and an aryl group

having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (ix) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below, (x) an aryloxy group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xi) an arylthio group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xii) an arylamino group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xiii) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xiv) an aralkyloxy group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xv) an aralkylthio group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xvi) an aralkylamino group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below on the aryl moiety, (xvii) a 1-pyrrolyl group,

(xviii) a 1-pyrrolidinyl group, (xix) a 1-imidazolyl group, (xx) a piperidino group or (xxi) a morpholino group,

$x^a$  represents an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below or a 5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms which may have from 1 to 3 substituents  $\alpha^a$  mentioned below,

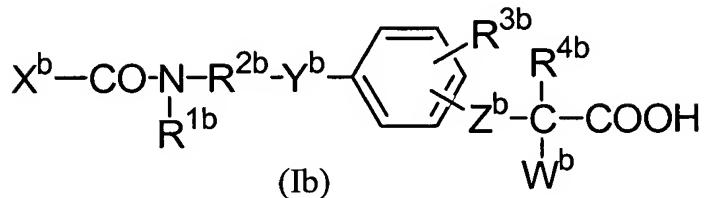
the substituent  $\alpha^a$  is selected from the group consisting of (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a straight- or branched-chain halogenated alkyl group having from 1 to 4 carbon atoms, (iii) a hydroxyl group, (iv) a straight- or branched-chain aliphatic acyloxy group having from 1 to 4 carbon atoms, (v) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (vi) a straight- or branched-chain alkylenedioxy group having from 1 to 4 carbon atoms, (vii) an aralkyloxy group having from 7 to 12 carbon atoms, (viii) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (ix) a straight- or branched-chain alkylsulfonyl group having from 1 to 4 carbon atoms, (x) a halogen atom, (xi) a nitro group, (xii) a straight-

or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (xiii) an aralkyl group having from 7 to 12 carbon atoms, (xiv) an aryl group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xv) an aryloxy group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvi) an arylthio group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4

carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvii) an arylsulfonyl group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xviii) an arylsulfonylamino group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms, and the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms), (xix) a 5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xx) a 5- to 10-membered monocyclic or bicyclic

heteroaromatic oxy group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxi) a 5- to 10-membered monocyclic or bicyclic heteroaromatic thio group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonyl group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms and (xxiii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonylamino group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms (the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms) and

$Y^a$  represents an oxygen atom, a sulfur atom or a group of formula:  $>N-R^{4a}$  (wherein  $R^{4a}$  represents a hydrogen atom, a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms or a straight- or branched-chain aliphatic acyl group having from 1 to 8 carbon atoms or an aromatic acyl group)], a amidocarboxylic acid derivative having the general formula (Ib) below:



a pharmacologically acceptable salt thereof or a  
pharmacologically acceptable ester thereof

[wherein,

$R^{1b}$  represents a hydrogen atom or a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms,

$R^{2b}$  represents a straight- or branched-chain alkylene group having from 1 to 6 carbon atoms,

$R^{3b}$  represents (i) a hydrogen atom, (ii) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (v) a halogen atom, (vi) a nitro group, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3

substituents  $\alpha^b$  mentioned below or (ix) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety,

$R^{4b}$  represents a hydrogen atom or a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms,

$Z^b$  represents a single bond or a straight- or branched-chain alkylene group having from 1 to 6 carbon atoms,

$W^b$  represents (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a hydroxyl group, (iii) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (iv) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (v) an amino group, (vi) a straight- or branched-chain monoalkylamino group having from 1 to 4 carbon atoms, (vii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (viii) an N-alkyl-N-arylamino group having a straight- or branched-chain alkyl group having from 1 to 4 carbon atoms and an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (ix) an aryl group having from 6 to 10 carbon atoms which may have from 1 to 3

substituents  $\alpha^b$  mentioned below, (x) an aryloxy group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xi) an arylthio group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xii) an arylamino group having from 6 to 10 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xiii) an aralkyl group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xiv) an aralkyloxy group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xv) an aralkylthio group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xvi) an aralkylamino group having from 7 to 12 carbon atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below on the aryl moiety, (xvii) a 1-pyrrolyl group, (xviii) a 1-pyrrolidinyl group, (xix) a 1-imidazolyl group, (xx) a piperidino group or (xxi) a morpholino group,  
 $\alpha^b$  represents an aryl group having from 6 to 10 carbon atoms

which may have from 1 to 3 substituents  $\alpha^b$  mentioned below or a 5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms which may have from 1 to 3 substituents  $\alpha^b$  mentioned below,

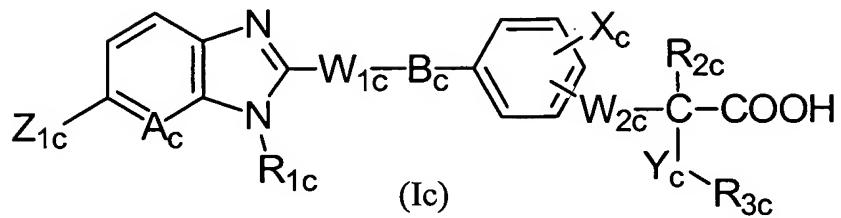
the substituent  $\alpha^b$  mentioned above is selected from the group consisting of (i) a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms, (ii) a straight- or branched-chain halogenated alkyl group having from 1 to 4 carbon atoms, (iii) a hydroxyl group, (iv) a straight- or branched-chain aliphatic acyloxy group having from 1 to 4 carbon atoms, (v) a straight- or branched-chain alkoxy group having from 1 to 4 carbon atoms, (vi) a straight- or branched-chain alkylenedioxy group having from 1 to 4 carbon atoms, (vii) an aralkyloxy group having from 7 to 12 carbon atoms, (viii) a straight- or branched-chain alkylthio group having from 1 to 4 carbon atoms, (ix) a straight- or branched-chain alkylsulfonyl group having from 1 to 4 carbon atoms, (x) a halogen atom, (xi) a nitro group, (xii) a straight- or branched-chain dialkylamino group in which the alkyl groups are the same or different from each other and each has from 1 to 4 carbon atoms, (xiii) an aralkyl group having from 7

to 12 carbon atoms, (xiv) an aryl group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xv) an aryloxy group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvi) an arylthio group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xvii) an arylsulfonyl group having from 6 to 10 carbon atoms (the aryl

moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms), (xviii) an arylsulfonylamino group having from 6 to 10 carbon atoms (the aryl moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms, a straight- or branched-chain halogenated alkyl having from 1 to 4 carbon atoms, a straight- or branched-chain alkoxy having from 1 to 4 carbon atoms, a halogen or a straight- or branched-chain alkylenedioxy having from 1 to 4 carbon atoms, and the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms), (xix) a 5- to 10-membered monocyclic or bicyclic heteroaromatic group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xx) a 5- to 10-membered monocyclic or bicyclic heteroaromatic oxy group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxi) a 5- to 10-membered monocyclic or bicyclic

heteroaromatic thio group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms, (xxii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonyl group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms and (xxiii) a 5- to 10-membered monocyclic or bicyclic heteroaromatic sulfonylamino group containing from 1 to 4 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur atoms (the nitrogen atom of the amino moiety may be substituted with a straight- or branched-chain alkyl having from 1 to 6 carbon atoms) and

$y^b$  represents an oxygen atom, a sulfur atom or a group of formula:  $>N-R^{5b}$  (wherein  $R^{5b}$  represents a hydrogen atom, a straight- or branched-chain alkyl group having from 1 to 6 carbon atoms or a straight- or branched-chain aliphatic acyl group having from 1 to 8 carbon atoms or an aromatic acyl group)], a  $\alpha$ -substituted carboxylic acid derivative having the general formula (Ic) below:



a pharmacologically acceptable ester thereof, a pharmacologically acceptable amide thereof or a pharmacologically acceptable salt thereof

[wherein,

$R_{1c}$ ,  $R_{2c}$  and  $R_{3c}$  are the same or different, and each represents (i) a hydrogen atom, (ii) a  $C_1$ - $C_6$  alkyl group, (iii) a  $C_6$ - $C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below), (iv) a  $C_7$ - $C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below on the aryl moiety), (v) a  $C_1$ - $C_6$  alkylsulfonyl group, (vi) a  $C_1$ - $C_6$  halogenoalkylsulfonyl group, (vii) a  $C_6$ - $C_{10}$  arylsulfonyl group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below) or (viii) a  $C_7$ - $C_{16}$  aralkylsulfonyl group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below on the aryl moiety),

$A_c$  represents a nitrogen atom or a =CH- group,

$B_c$  represents an oxygen atom or a sulfur atom,

$W_{1c}$  represents a  $C_1$ - $C_8$  alkylene group,

$W_{2c}$  represents a single bond or a  $C_1$ - $C_8$  alkylene group,

$X_c$  represents (i) a hydrogen atom, (ii) a  $C_1$ - $C_6$  alkyl group, (iii) a  $C_1$ - $C_6$  halogenoalkyl group, (iv) a  $C_1$ - $C_6$  alkoxy group, (v) a halogen atom, (vi) a hydroxyl group, (vii) a cyano group, (viii) a nitro group, (ix) a  $C_3$ - $C_{10}$  cycloalkyl group, (x) a  $C_6$ - $C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (xi) a  $C_7$ - $C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety), (xii) a  $C_1$ - $C_7$  aliphatic acyl group, (xiii) a  $C_4$ - $C_{11}$  cycloalkylcarbonyl group, (xiv) a  $C_7$ - $C_{11}$  arylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (xv) a  $C_8$ - $C_{17}$  aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety), (xvi) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (xvii) a carbamoyl group, (xviii) a  $C_7$ - $C_{11}$  arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety) or (xix) an amino group (optionally having one or two substituents  $\beta_c$  mentioned below),

$Y_c$  represents an oxygen atom or a  $S(O)_p$  group (wherein p is an integer of from 0 to 2),

$Z_{1c}$  represents (i) a hydrogen atom, (ii) a  $C_1-C_6$  alkyl group, (iii) a  $C_1-C_6$  alkoxy group, (iv) a  $C_1-C_6$  alkylthio group, (v) a halogen atom, (vi) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\alpha_1$  mentioned below), (vii) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below on the aryl moiety), (viii) a  $C_6-C_{10}$  aryloxy group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below), (ix) a  $C_7-C_{16}$  aralkyloxy group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below on the aryl moiety), (x) a  $C_3-C_{10}$  cycloalkyloxy group, (xi) a  $C_3-C_{10}$  cycloalkylthio group, (xii) a saturated heterocyclic oxy group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below), (xiii) a monocyclic heteroaromatic oxy group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below), (xiv) a  $C_6-C_{10}$  arylthio group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below), (xv) a  $C_7-C_{16}$  aralkylthio group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below on the aryl moiety), (xvi) a saturated heterocyclic thio group (optionally having from 1 to 5

substituents  $\alpha_{1c}$  mentioned below), (xvii) a monocyclic heteroaromatic thio group (optionally having from 1 to 5 substituents  $\alpha_{1c}$  mentioned below), (xviii) an amino group (optionally having one or two substituents  $\alpha_{1c}$  mentioned below) or (xix) a hydroxyl group,

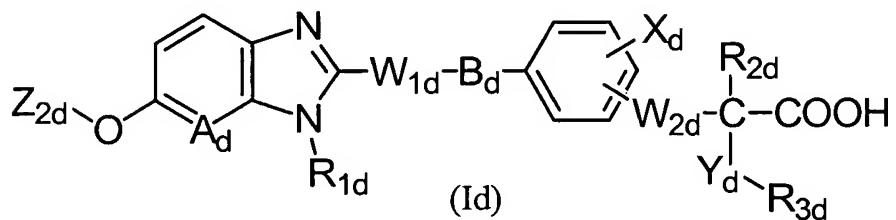
the substituent  $\alpha_{1c}$  represents (i) a C<sub>1</sub>-C<sub>6</sub> alkyl group, (ii) a C<sub>1</sub>-C<sub>6</sub> halogenoalkyl group, (iii) a C<sub>1</sub>-C<sub>6</sub> alkoxy group, (iv) a halogen atom, (v) a hydroxyl group, (vi) a cyano group, (vii) a nitro group, (viii) a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, (ix) a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (x) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety), (xi) a C<sub>1</sub>-C<sub>7</sub> aliphatic acyl group, (xii) a C<sub>4</sub>-C<sub>11</sub> cycloalkylcarbonyl group, (xiii) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (xiv) a C<sub>8</sub>-C<sub>11</sub> aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety), (xv) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below), (xvi) a carbamoyl group, (xvii) a C<sub>7</sub>-C<sub>11</sub>

arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\beta_c$  mentioned below on the aryl moiety), (xviii) an amino group (optionally having one or two substituents  $\beta_c$  mentioned below) or (xix) a carboxyl group,

the substituent  $\beta_c$  represents (i) a  $C_1-C_{10}$  alkyl group, (ii) a halogen atom, (iii) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below), (iv) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below on the aryl moiety), (v) a  $C_1-C_7$  aliphatic acyl group, (vi) a  $C_7-C_{11}$  arylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below), (vii) a  $C_8-C_{17}$  aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below on the aryl moiety), (viii) a  $C_4-C_{11}$  cycloalkylcarbonyl group, (ix) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below), (x) a carbamoyl group or (xi) a  $C_7-C_{11}$  arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\gamma_c$  mentioned below on the aryl moiety) and

the substituent  $\gamma_c$  represents a  $C_1-C_6$  alkyl group, a  $C_1-C_6$

halogenoalkyl group, a halogen atom or a hydroxyl group],  
a  $\alpha$ -substituted carboxylic acid derivative having the  
general formula (Id) below:



a pharmacologically acceptable ester thereof, a pharmacologically acceptable amide thereof or a pharmacologically acceptable salt thereof

[wherein,

$R_{1d}$ ,  $R_{2d}$  and  $R_{3d}$  are the same or different, and each represents (i) a hydrogen atom, (ii) a  $C_1$ - $C_6$  alkyl group, (iii) a  $C_6$ - $C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\alpha_{1d}$  mentioned below), (iv) a  $C_7$ - $C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\alpha_{1d}$  mentioned below on the aryl moiety), (v) a  $C_1$ - $C_6$  alkylsulfonyl group, (vi) a  $C_1$ - $C_6$  halogenoalkylsulfonyl group, (vii) a  $C_6$ - $C_{10}$  arylsulfonyl group (optionally having from 1 to 5 substituents  $\alpha_{1d}$  mentioned below)

or (viii) a C<sub>7</sub>-C<sub>16</sub> aralkylsulfonyl group (optionally having from 1 to 5 substituents α<sub>1d</sub> mentioned below on the aryl moiety),

A<sub>d</sub> represents a nitrogen atom or a =CH- group,

B<sub>d</sub> represents an oxygen atom or a sulfur atom,

W<sub>1d</sub> represents a C<sub>1</sub>-C<sub>8</sub> alkylene group,

W<sub>2d</sub> represents a single bond or a C<sub>1</sub>-C<sub>8</sub> alkylene group,

X<sub>d</sub> represents (i) a hydrogen atom, (ii) a C<sub>1</sub>-C<sub>6</sub> alkyl group, (iii) a C<sub>1</sub>-C<sub>6</sub> halogenoalkyl group, (iv) a C<sub>1</sub>-C<sub>6</sub> alkoxy group, (v) a halogen atom, (vi) a hydroxyl group, (vii) a cyano group, (viii) a nitro group, (ix) a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, (x) a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below), (xi) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below on the aryl moiety), (xii) a C<sub>1</sub>-C<sub>7</sub> aliphatic acyl group, (xiii) a C<sub>4</sub>-C<sub>11</sub> cycloalkylcarbonyl group, (xiv) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below), (xv) a C<sub>8</sub>-C<sub>17</sub> aralkylcarbonyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below on the aryl moiety), (xvi) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below), (xvii) a carbamoyl

group, (xviii) a C<sub>7</sub>-C<sub>11</sub> arylaminocarbonyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below on the aryl moiety) or (xix) an amino group (optionally having one or two substituents β<sub>d</sub> mentioned below),

Y<sub>d</sub> represents an oxygen atom or a S(O)<sub>p</sub> group (wherein p is an integer of from 0 to 2),

Z<sub>2d</sub> represents a saturated heterocyclic group (optionally having from 1 to 5 substituents α<sub>1d</sub> mentioned below) or a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents α<sub>2d</sub> mentioned below),

the substituent α<sub>1d</sub> represents (i) a C<sub>1</sub>-C<sub>6</sub> alkyl group, (ii) a C<sub>1</sub>-C<sub>6</sub> halogenoalkyl group, (iii) a C<sub>1</sub>-C<sub>6</sub> alkoxy group, (iv) a halogen atom, (v) a hydroxyl group, (vi) a cyano group, (vii) a nitro group, (viii) a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, (ix) a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below), (x) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below on the aryl moiety), (xi) a C<sub>1</sub>-C<sub>7</sub> aliphatic acyl group, (xii) a C<sub>4</sub>-C<sub>11</sub> cycloalkylcarbonyl group, (xiii) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group (optionally having from 1 to 5 substituents β<sub>d</sub> mentioned below), (xiv) a C<sub>8</sub>-C<sub>17</sub> aralkylcarbonyl

group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below on the aryl moiety), (xv) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below), (xvi) a carbamoyl group, (xvii) a C<sub>7</sub>-C<sub>11</sub> arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below on the aryl moiety), (xviii) an amino group (optionally having one or two substituents  $\beta_d$  mentioned below) or (xix) a carboxyl group,

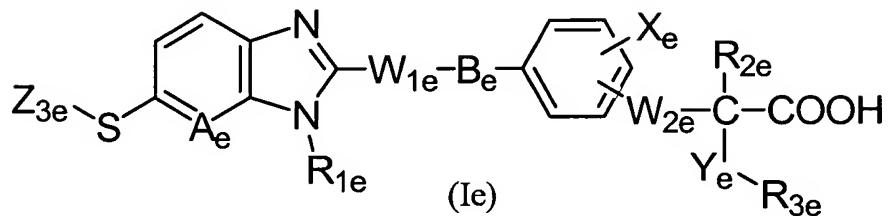
the substituent  $\alpha_{2d}$  represents (i) a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, (ii) a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below), (iii) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below on the aryl moiety), (iv) a C<sub>1</sub>-C<sub>7</sub> aliphatic acyl group, (v) a C<sub>4</sub>-C<sub>11</sub> cycloalkylcarbonyl group, (vi) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below), (vii) a C<sub>8</sub>-C<sub>17</sub> aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below on the aryl moiety), (viii) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below) or (ix) a C<sub>7</sub>-C<sub>11</sub>

arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\beta_d$  mentioned below on the aryl moiety),

the substituent  $\beta_d$  represents (i) a  $C_1-C_{10}$  alkyl group, (ii) a halogen atom, (iii) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below), (iv) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below on the aryl moiety), (v) a  $C_1-C_7$  aliphatic acyl group, (vi) a  $C_7-C_{11}$  arylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below), (vii) a  $C_8-C_{17}$  aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below on the aryl moiety), (viii) a  $C_4-C_{11}$  cycloalkylcarbonyl group, (ix) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below), (x) a carbamoyl group or (xi) a  $C_7-C_{11}$  arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\gamma_d$  mentioned below on the aryl moiety) and

the substituent  $\gamma_d$  represents a  $C_1-C_6$  alkyl group, a  $C_1-C_6$  halogenoalkyl group, a halogen atom or a hydroxyl group] and a  $\alpha$ -substituted carboxylic acid derivative having the

general formula (Ie) below:



a pharmacologically acceptable ester thereof, a pharmacologically acceptable amide thereof or a pharmacologically acceptable salt thereof

[wherein,

$R_{1e}$ ,  $R_{2e}$  and  $R_{3e}$  are the same or different, and each represents (i) a hydrogen atom, (ii) a  $C_1$ - $C_6$  alkyl group, (iii) a  $C_6$ - $C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below), (iv) a  $C_7$ - $C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below on the aryl moiety), (v) a  $C_1$ - $C_6$  alkylsulfonyl group, (vi) a  $C_1$ - $C_6$  halogenoalkylsulfonyl group, (vii) a  $C_6$ - $C_{10}$  arylsulfonyl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below) or (viii) a  $C_7$ - $C_{16}$  aralkylsulfonyl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below on the aryl moiety),

A<sub>e</sub> represents a nitrogen atom or a =CH- group,  
B<sub>e</sub> represents an oxygen atom or a sulfur atom,  
W<sub>1e</sub> represents a C<sub>1</sub>-C<sub>8</sub> alkylene group,  
W<sub>2e</sub> represents a single bond or a C<sub>1</sub>-C<sub>8</sub> alkylene group,  
X<sub>e</sub> represents (i) a hydrogen atom, (ii) a C<sub>1</sub>-C<sub>6</sub> alkyl group,  
(iii) a C<sub>1</sub>-C<sub>6</sub> halogenoalkyl group, (iv) a C<sub>1</sub>-C<sub>6</sub> alkoxy group, (v)  
a halogen atom, (vi) a hydroxyl group, (vii) a cyano group,  
(viii) a nitro group, (ix) a C<sub>3</sub>-C<sub>10</sub> cycloalkyl group, (x) a C<sub>6</sub>-C<sub>10</sub>  
aryl group (optionally having from 1 to 5 substituents β<sub>e</sub>  
mentioned below), (xi) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having  
from 1 to 5 substituents β<sub>e</sub> mentioned below on the aryl moiety),  
(xii) a C<sub>1</sub>-C<sub>7</sub> aliphatic acyl group, (xiii) a C<sub>4</sub>-C<sub>11</sub>  
cycloalkylcarbonyl group, (xiv) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group  
(optionally having from 1 to 5 substituents β<sub>e</sub> mentioned below),  
(xv) a C<sub>8</sub>-C<sub>17</sub> aralkylcarbonyl group (optionally having from 1 to 5  
substituents β<sub>e</sub> mentioned below on the aryl moiety), (xvi) a  
monocyclic heteroaromatic carbonyl group (optionally having from  
1 to 5 substituents β<sub>e</sub> mentioned below), (xvii) a carbamoyl  
group, (xviii) a C<sub>7</sub>-C<sub>11</sub> arylaminocarbonyl group (optionally having  
from 1 to 5 substituents β<sub>e</sub> mentioned below on the aryl moiety)

or (xix) an amino group (optionally having one or two substituents  $\beta_e$  mentioned below),

$Y_e$  represents an oxygen atom or a  $S(O)_p$  group (wherein p is an integer of from 0 to 2),

$Z_{3e}$  represents (i) a  $C_1-C_6$  alkyl group, (ii) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below), (iii) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below on the aryl moiety), (iv) a  $C_3-C_{10}$  cycloalkyl group or (v) a saturated heterocyclic group (optionally having from 1 to 5 substituents  $\alpha_{1e}$  mentioned below),

the substituent  $\alpha_{1e}$  represents (i) a  $C_1-C_6$  alkyl group, (ii) a  $C_1-C_6$  halogenoalkyl group, (iii) a  $C_1-C_6$  alkoxy group, (iv) a halogen atom, (v) a hydroxyl group, (vi) a cyano group, (vii) a nitro group, (viii) a  $C_3-C_{10}$  cycloalkyl group, (ix) a  $C_6-C_{10}$  aryl group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below), (x) a  $C_7-C_{16}$  aralkyl group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below on the aryl moiety), (xi) a  $C_1-C_7$  aliphatic acyl group, (xii) a  $C_4-C_{11}$  cycloalkylcarbonyl group, (xiii) a  $C_7-C_{11}$  arylcarbonyl group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below), (xiv) a  $C_8-C_{17}$  aralkylcarbonyl

group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below on the aryl moiety), (xv) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below), (xvi) a carbamoyl group, (xvii) a C<sub>7</sub>-C<sub>11</sub> arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\beta_e$  mentioned below on the aryl moiety), (xviii) an amino group (optionally having one or two substituents  $\beta_e$  mentioned below) or (xix) a carboxyl group,

the substituent  $\beta_e$  represents (i) a C<sub>1</sub>-C<sub>10</sub> alkyl group, (ii) a halogen atom, (iii) a C<sub>6</sub>-C<sub>10</sub> aryl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below), (iv) a C<sub>7</sub>-C<sub>16</sub> aralkyl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below on the aryl moiety), (v) a C<sub>1</sub>-C<sub>7</sub> aliphatic acyl group, (vi) a C<sub>7</sub>-C<sub>11</sub> arylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below), (vii) a C<sub>8</sub>-C<sub>17</sub> aralkylcarbonyl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below on the aryl moiety), (viii) a C<sub>4</sub>-C<sub>11</sub> cycloalkylcarbonyl group, (ix) a monocyclic heteroaromatic carbonyl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below),

(x) a carbamoyl group or (xi) a C<sub>7</sub>-C<sub>11</sub> arylaminocarbonyl group (optionally having from 1 to 5 substituents  $\gamma_e$  mentioned below on the aryl moiety) and

the substituent  $\gamma_e$  represents a C<sub>1</sub>-C<sub>6</sub> alkyl group, a C<sub>1</sub>-C<sub>6</sub> halogenoalkyl group, a halogen atom or a hydroxyl group].

**13. (Withdrawn)** A method according to claim 12, wherein said diuretic comprises one or more compounds selected from the group consisting of acetazolamide, azosemide, amiloride[], and isosorbide, etacrynic acid, potassium canrenoate, chlortalidone, cyclopentiazide, spironolactone, torasemide, triamterene[], trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, piretanide, bumetanide, furosemide, benzylhydrochlorothiazide, penflutizide, methyclothiazide, metolazone and mefruside.

**14. (Withdrawn)** A method according to claim 8, wherein said insulin sensitiser sensitizer is 5-[4-(6-methoxy-1-methyl-1H-benzimidazol-2-ylmethoxy)benzyl]thiazolidine-2,4-dione or a pharmacologically acceptable salt thereof.

15. (Withdrawn) A method according to claim 14, wherein said diuretic ~~comprises one or more compounds selected from the group consisting of ENaC inhibitors~~ is triamterene.

16. (Withdrawn) A method according to claim 14, wherein said diuretic is amiloride.

17. (Withdrawn) A method for the prophylaxis of edema, cardiac enlargement, body fluid retention, or hydrothorax caused by an insulin sensitizer comprising administering an effective amount of the pharmaceutical composition of claim 1.

18. (Withdrawn) A method according to claim 17, wherein said diuretic ~~is comprises one or more compounds selected from the group consisting of acetazolamide, azosemide, amiloride, isosorbide, etacrynic acid, potassium canrenoate, chlortalidone, cyclopentiazide, spironolactone, torasemide, triamterene[[],] trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, piretanide, bumetanide, furosemide, benzylhydrochlorothiazide, penflutiazide, methyclothiazide, metolazone and mefruside.~~

**Claim 19 (Canceled).**

**20. (Withdrawn)** A method according to claim 17, wherein said diuretic is amiloride.

**21. (New)** A pharmaceutical composition according to claim 2, wherein said diuretic is triamterene.